JMSCR Vol||05||Issue||02||Pages 17926-17939||February 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i2.118

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Urinary Neutrophil Gelatinase Associated Lipocalin as a Biomarker for Diagnosis and Prognosis of Acute Kidney Injury (AKI) in Cirrhotic Patients

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Abstract

Introduction: *Acute kidney injury is associated with increased mortality in hospitalized cirrhotic patients; therefore early and accurate diagnosis is crucial. The prognosis of AKI in cirrhosis depends on its specific aetiology which remains a challenge.*

Aim: *We aimed to determine the accuracy of urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) for diagnosis, differentiation of the various aetiologies of AKI in cirrhotics and to evaluate its value in short term prognosis.*

Methods: *Eighty-two cirrhotic patients were investigated for uNGAL during hospital admission and AKI types were determined blinded to uNGAL measurements. Patients were followed up till discharge.*

Results: *Patients with liver cirrhosis and renal impairment (n= 62) had significantly higher levels of uNGAL (102.4 ±100 ng/ml) when compared with patients with cirrhotics with normal kidney function (n= 20) (102.4 ±100 vs 17.4±14.71 ng/ml). Patients with acute tubular necrosis (ATN) had significantly higher uNGAL (189.2±124 ng/ml) compared to other aetiologies, while prerenal azotemia had the lowest value (46.1±39.9 ng/ml). UNGAL levels were significantly higher in the mortality group of patients (p=0.006) and in patients admitted to ICU (p<0.001) than the survivors and patient without ICU admission respectively. The AUC of uNGAL for diagnosis of AKI was 0.892 with a cutoff > 33 ng/ml providing specificity 90% and sensitivity 79%. In multivariate regression analysis, uNGAL was highly significant independent predictor of inpatient cirrhosis relayed mortality.*

Conclusion: *UNGAL is a promising biomarker for diagnosis of AKI and differentiation between its different aetiologies in cirrhosis including ATN, HRS and pre renal azotemia. UNGAL can independently predict poor short term prognosis.*

Keywords: *AKI: Acute kidney injury, NGAL : Urinary neutrophil gelatinase associated lipocalin , cirrhosis, ATN: Acute tubular necrosis , HRS: Hepatorenal syndrome.*

Introduction

Acute impairment of kidney function is very common in patients with advanced cirrhosis [1,2]. Up to 20% of hospitalized patients with cirrhosis develop AKI [3–5] and once AKI occurs there is a reported 4-fold increased risk of mortality [2]. The most common causes of acute impairment of kidney function are pre-renal azotemia due to volume depletion, acute tubular necrosis (ATN), hepatorenal syndrome (HRS), and nephrotoxicity, mainly due to non-steroidal anti-inflammatory drugs (NSAIDs) [6]. While ATN is characterized by alterations in kidney tubular cells [7-9], HRS is due to functional impairment of kidney function related to intense vasoconstriction of the kidney circulation in the absence of significant histology-

ical lesions [1,10,11]. The diagnosis of these causes relies on diagnostic criteria which include some degree of subjectivity [12] and unfortunately serum creatinine (sCr), the clinical standard to define kidney function, poorly discriminates AKI causes in cirrhosis [13-15]. The differential diagnosis between HRS and ATN is particularly challenging. This, added to the complexity of severely-ill patients with cirrhosis, makes the diagnosis of the cause of acute impairment of kidney function uncertain in some cases. Besides acute impairment of kidney function, patients with cirrhosis may also develop chronic kidney diseases (CKD) either related to the liver disease itself or extrahepatic conditions [16-18]. The differential diagnosis of the causes of acute impairment of kidney function in cirrhosis is important to apply specific therapies for each cause. Pre-renal azotemia should be treated with plasma volume expansion, while this is not effective and may be even deleterious in patients with ATN [19]. Besides, there is currently an effective pharmacological treatment of HRS [18, 20]. Therefore, there is an urgent need for objective methods in the differential diagnosis of impairment of kidney function in cirrhosis.

In the last years, there has been a major interest to investigate kidney biomarkers either in the urine or plasma, which are released at the time of injury of tubular cells and could be used for an early diagnosis of acute kidney injury and also for differential diagnosis between ATN and other causes of impairment of kidney function [21, 22]. Among them, NGAL has received a great deal of attention. However, the existing studies on its potential usefulness in the differential diagnosis of impairment of kidney function in cirrhosis are scant [23, 24].

A number of them have shown that uNGAL levels are markedly increased in patients with ATN compared to those of patients with pre-renal azotemia and non-progressive CKD, suggesting that uNGAL may be used for the differential diagnosis of the cause of acute kidney injury [23,25]. Another stated that uNGAL predicts the development of kidney injury in different clinical settings, and may also be helpful in the prediction of the need for dialysis and early mortality especially in cirrhotic patients [25-27].

Patients and Methods

Study Protocol

This study included 82 cirrhotic patients admitted to the hepatology and gastroenterology unit of Assiut university hospital. The majority of patients were males n=60 (73%) and 22 were females (27%). Cirrhosis definition was based on the presence of clinical, biochemical or structural abnormalities consistent with liver cirrhosis in addition to abnormal Child-Pough and MELD scores. Impairment of kidney function was defined according to Acute Kidney Injury Network (AKIN) criteria based on change in SCr and / or Urine output [28]. Exclusion of Patients was for the presence of urinary tract infection, after kidney or liver transplant and Patients on regular hemodialysis.

Patients were divided into three groups as shown in figure 1 according to the stages of liver cirrhosis. Group III included 62 patients with liver cirrhosis and impaired kidney function with or without ascites were further subdivided into four categories according to the etiology of renal impairment. Patients were followed up during their hospital stay for short term prognosis in form of the need for ICU admission, need for dialysis session or inpatients mortality related to liver cirrhosis.

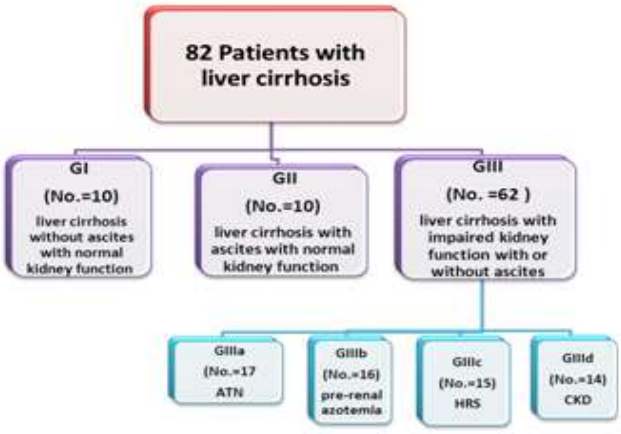

Figure (1)

Operational Definitions

I. Acute tubular necrosis (ATN) was diagnosed by 1-history suggestive of an etiology.

2- Urinary sodium >40 mEq/L, 3- Fractional sodium excretion in urine >2%, 4- Urinary sediment as renal tubular epithelial cells, granular or brown granular casts.

II. Pre-renal Azotemia diagnosed by suggesting history of volume depletion and prospectively with improvement kidney function with fluid replacement or with fractional sodium excretion <1%.

III. Hepatorenal syndrome diagnosed according to Revised Diagnostic Criteria for hepatorenal syndrome modified as follows [29]:

1- Cirrhosis with ascites, 2- Serum creatinine > 1.5 mg/dl (133umol/l), 3- Absence of shock, 4- No improvement in seum creatinine (decrease to a level of 1.5 mg/dl) after at least 2days with diuretics withdrawal and volume expansion with albumin, 5- No current or recent treatment with nephrotoxic drugs and 6- Absence of parenchymal disease (abnormal Ultrasound, >50RBCs in urine/hpf or proteinuria >500mg/ day).

IV. Chronic kidney disease (CKD): diagnosed by the presence of altered kidney function >3 month or radiological evidence of structurally diseased kidneys.

Methods

After obtaining written consent from all patients involved in this study with ethical committee approval of faculty of medicine, Assiut Univer-rsity, all involved patients were subjected to complete history taking, thorough clinical examination and assessment of severity of cirrhosis according to Child-Turcotte- Pugh classification [30], system and MELD scores [31]. For all patients, the following investigations were done Complete urine analysis, measurement of urinary proteins in 24 hours urine collection for protienuric patients, urinary creatinine and micro-albumin were semi quantified by specified urine strips, urinary sodium, fractional sodium excretion in urine was calculated by *FENa = 100 × (urinary sodium × serum creatinine) / serum sodium × urinary creatinine [Sodium (mmol/l) Creatinine (mg/dl)]* [32], Serum urea and creatinine, serum electrolytes (Calcium, Sodium, Potassium, Phosphorus and Magnesium), GFR calculated with MDRD equation, complete liver function tests, Prothrombin Concentration, prothrombin time and INR, hepatitis markers (HCV antibody, HBsAg), ascitic fluid study, blood cultures when indicated, complete blood picture and abdominal ultrasound. Estimation of uNGAL was done by ELISA kit (Catalog no. E-EL-H0096, Elabscience Biotechnology Co., Ltd). This was done by specialists in the Laboratory of Clinical Immunology, Assiut University Hospital. The specialists were blinded to patient diagnosis and group classification.

Statistical Analysis

Statistical analysis were performed with the IBM SPSS 20.0 software. The data were tested for normality using the Anderson-Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean, SD). Chi-square test used to compare between categorical variables where compare between continuous variables by t-test and ANOVA. ROC curve used to determine the cutoff value. Pearson correlation coefficient used to assess the association between continuous variables. A two-tailed $p < 0.05$ was considered statistically significant. Correlation between categorical variables was performed in 2x2 contingency tables. Comparison between metric variables was done using non parametric tests (Mann-Whitney test and Wilcoxon signed ranks test). Multivariable analysis was done using backward stepwise logistic regression. Exact p value (2-sided) was calculated and a value ≤ 0.05 was considered statistically significant.

Results

Characteristics of the patient population

Eighty two patients were enrolled in this study. Their ages ranged from 40 to 79 years with mean±SD = 57.6±9.35. Sixty patients (73%) were males and 22 were females (27%). The most common aetiology of cirrhosis was HCV infection in (77%) of patients, followed by HBV infection in (6%), other causes of cirrhosis included autoimmune hepatitis, budd-chiari syndrome and cryptogenic cirrhosis. Eleven patients (13%) had malignancies which included hepatocellular carcinoma (HCC), cholangiocarcinoma, lymph-oma, choriocarcinoma and metastasis of unkown origin. The majority of patients (80%) were admitted for complication of cirrhosis, including ascites (26%), hepatic encephalopathy (35%), GIT bleeding (13%) and HCC (6%). The laboratory and clinical data for all the groups were shown in table 1. None of the traditional kidney biomarkers showed significant statistical difference among different subgroups of patients with impaired kidney function as illustrared in table 2.

Table 1: Laboratory and clinical data among the studied groups of patients:

mean±SD	GI & II (n=20)	GIII (n=62)	P. value
WBCs (10^3xuL)	8.8±4.9	10±5.6	0.400
Hb (g/dL)	9.8±2.2	10±1.9	0.622
MCV (fl)	83.2±10.6	89.5±9.2	**0.013***
PLT (/10^3)	155±118.8	130.7±86.9	0.327
PC (%)	58.0±13.3	49.9±13.5	**0.026***
ALT (U/L)	41.3±21.8	92.2±140.2	0.111
AST (U/L)	72.6±42.2	130.5±232.6	0.273
Alb (g/dL)	2.51±0.75	2.09±0.59	**0.017***
ALP (U/L)	160±153.2	183.6±189.7	0.614
TP (g/dL)	6.05±0.85	5.7±0.78	0.115
T Bil (mg/dL)	59±94.7	128.1±139.8	**0.043***
Na (mEq/L)	137.9±8.0	131.3±8.3	**0.003****
K (mEq/L)	4±0.9	4.7±1.1	**0.010****
Ca (mg/dL)	9.4±0.6	8.9±1.1	0.098
PO4 (mg/dL)	3.4±0.9	5.7±2.8	**0.001****
Mg (mg/dL)	1.9±0.3	2.3±0.5	**0.001****
MELD score	14.3±5.45	26.8±9.1	**0.000****
Child- Turcotte- Pugh score	9.3±1.78	11.0±1.6	**0.000****

*Statistically significant difference ($p<0.05$) **Statistically highly significant difference ($p<0.01$)
(WBCs): white blood cells, (Hg): hemoglobin, (MCV): mean corpuscular volume, (PC): prothrombin concentration, (Na): sodium, (K): potassium, (Ca): calcium, (PO4): phosphorus, (Mg): magnesium, (ALT): alanine transaminase, (AST): aspartate transaminase, (Alb): albumin, (ALP): alkaline phosphatase, (TP): total protein, (TBil): total bilirubin.

Table 2: kidney function tests among patients with liver cirrhosis and impaired kidney function:

Kidney function	Patients with liver cirrhosis and impaired kidney function (GIII) (No=62) mean±SD				
	Total	ATN (n=17)	Prerenal azotemia (n=16)	HRS (n=15)	CKD (n=14)
Serum creatinine (umol/l)	282.2±248. 8	291±156.7	365.9±403.9	400.6±222.3	305±172.8
Serum urea (mmol/l)	24.1±15.6	29.5±15.1	29±19.8	33.1±11.7	19.4±7.3
Urinary Sodium	80.9±28.93	80.24±23.74	76.67±22.18	78.67±27.41	84.86±33.07
FENa (%)	2.3±2.8	1.8±1.3	2.6±3.3	3.3±3.6	3.4±3.8
Urine analysis: urine RBCs (/hpf)	26.9±132.7	14±20.4	18.1±39.6	4.6±2.5	94.1±297.5
Urine Pus (/hpf)	9.6±20.2	9.6±20.4	13.2±27.2	6.2±2.8	11.1±21.2
Urinary creatinine (mg/dL)	116.9±72.6	150±122.5	200±117.6	250.3±218.5	55±63.6
Microalbumin (mg/L)	50.9±55.1	80.8±48.7	87.1±60.4	78.9±59.4	97.3±60.5
CrCl by MDRD	40.0±32.5	30.7±25.5	29.7±20.5	18.6±8.4	28.2±21.6
Urinary Protein (mg/24 hour)	519.8±604.2	722.9±879.8	515.3±403.7	310.7±140.7	967.4±755.9

(RBCs): red blood cells; hpf, high power field, (FENa): fractional sodium excretion, (CrCl): creatinine clearance, (MDRD): Modification of Diet in Renal Disease.

Neutrophil gelatinase associated lipocalin results:

Patients with impairment of kidney function had significantly higher uNGAL levels (102.4 ±100 ng/ml) compared to those of patients without impairment of kidney function, either with or without ascites (figure 2). When patients with renal impaiement were categorized into 4 subgroups according to aetiology of renal impairment, patient with ATN had significantly higher level (mean± SD=189.2 ±124 ng/ml) as compared to other subgroups, followed by patients with CKD (mean± SD=73.6 ±70.7ng/ml), followed by patients with HRS (mean± SD=91.1±76 ng/ml) and the lowest value was for prerenal azotemia (mean± SD=46.1±39.9ng/ml). UNGAL levels were significantly higher (p<0.009) in patients with CKD with acute exacerbation compared with those with stable CKD.

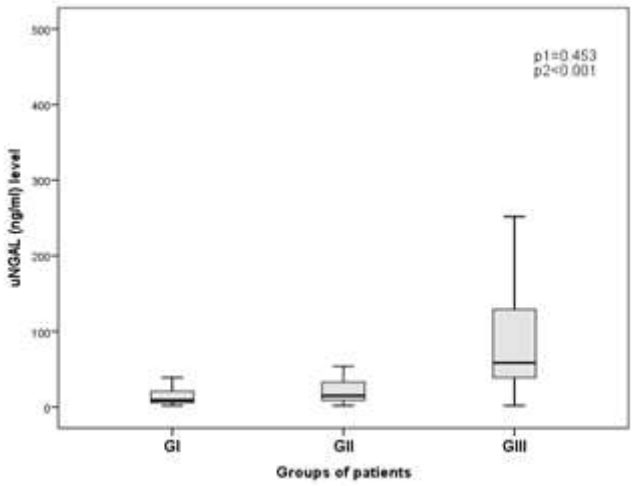

Figure 2: Mean ±SD of uNGAL levels among all the studied groups
P1: GI vs. GII
P2: GIII vs. GI and GII

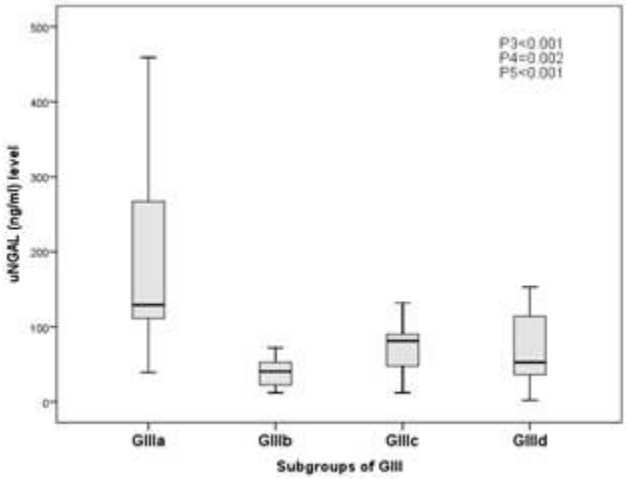

Figure 3: M ean±SD of uNGAL levels among GIII (patients with liver cirrhosis and impaired kidney functions
P3: GIIIa vs. GIIIb P4: GIIIa vs. GIIIc
P5: GIIIa vs. GIIId

In all the studied groups, patients with infections other than UTI (n = 36) had uNGAL levels higher than those of patients without infection (n = 46), but the difference did not reach statistical significance (table 3). Correlations between uNGAL levels and other parameters are shown in table 4. Patients with renal impairment without malignancies had significantly higher levels of uNGAL compared to those with malignancies.

Table 3: UNGAL level among all studied groups of patients as regard to the presence of infection other than urinary tract infection:

	Total No (No=82)	uNGAL (ng/ml)					
		GI (No=10)		GII (No=10)		GIII (No=62)	
		No	(mean±SD)	No	(mean±SD)	No	(mean±SD)
Patients without infection	46	8	13.3±12.3	4	15±8.5	34	92.35±89.45
Patients with infection	36	2	21±16.9	6	21.2±18.5	28	109.47±110.79
P. value		**0.401**		**0.889**		**0.647**	

Table 4: Correlations between levels of uNGAL and other indices among all groups of patients:

Variable	uNGAL (ng/ml)	
	R	P. value
Urine Volume	-0.195	0.080
Cr	0.148	0.183
Urea	0.221	**0.046***
CrCl by MDRD	-0.317	**0.004***
MELD score	0.126	0.259
Child – Pugh score	0.140	0.214
Microalbumin	0.17	0.127

(Cr): creatinine, (CrCl): creatinine clearance, (MDRD): modification of diet in renal disease, (MELD): model of end stage liver disease.

Short term prognosis results among patients with renal impairment were shown in table 5. Forty four of patients with renal impairment required ICU admission. Of them 13 patients were admitted for hemoynamic instability, 17 patients with grade III or IV (profound) encephalopathy, 9 patients with massive GIT bleeding,, and 5 patients with worsening kidney functions. Their uNGAL showed significant ($p<0.006$) increased level compared with those ont admitted to ICU. There were 34 (41%) deaths among group GIII during their hospital stay. There was significant ($p<0.017$) increased uNGAL level among them compared to discharged patients. Seven patients were referred to hemodialysis sessions before their deaths.

Table 5: UNGAL level among patients with renal impairment as regard to short term prognosis:

	GIII (n=62)		
	No (%)	uNGAL (mean±SD)	P value
No requery for ICU admission	18 (27)	51.1±41.9	0.006**
Requery for ICU admission	44 (73)	125.14±109.5	
Discharge	28 (45)	70.7±54.6	0.017*
Inpatient mortality	34 (55)	130.4±121.1	

The diagnostic and predictive value of uNGAL in diagnosis of AKI and more precisely diagnosis of ATN in patient with liver cirrhosis and its ability for prediction of poor short term prognosis are shown in table 6.

Table 6: the Value of uNGAL for diagnosis and prognosis of AKI in liver cirrhosis:

	Diagnosis of AKI	prediction of poor prognosis	Diagnosis of ATN
Cutoff value	>33	>57	>94
Sensitivity	79.0	63.6	82.2
Specificity	90.0	79.6	87.7
Positive predictive value	96.1	67.7	63.6
Negative predictive value	58.1	76.5	95
Area under the curve	0.892	0.740	0.887
Accuracy	85%	71.5%	80%

Univariate regression analysis to evaluate the association of uNGAL, serum creatinine, MELD and Child-Pugh scores with short term patient mortality, showed that all were significantly associated with short term mortality. But in multivariate regression analysis of them, uNGAL was highly significant independent predictor of mortality.

Table 7: Univariate and multivariate logistic regression analysis to predict short term mortality

	Univariate analysis		Multivariate analysis	
	Odds (95% CI)	P. value	Odds (95% CI)	P. value
uNGAL>57ng/ml	5(1.93-12.97)	0.001**	6.48(1.94-21.64)	0.002**
SCr	1.01(1-1.01)	0.001**	1(1-1.01)	0.080
MEID score	1.12(1.05-1.19)	0.001**	1.05(0.97-1.13)	0.258
Child-Pugh score	1.78(1.28-2.47)	0.001**	1.67(1.05-2.66)	0.030*

Discussion

In this study the number of cirrhotic males was more than females (73% vs 27% respectively). Among the different underlying aetiologies of liver cirrhosis, this study revealed that HCV was the commonest (77%) aetiology of liver cirrhosis. This finding was similar to those reported by *Yehia* who studied the prevalence of HCV in Egypt in 2011 [33], Also, in accordance with *El-Bassat et al* who studied NGAL among cirrhotic patients in Tanta University in 2013 and reported that HCV was the commonest aetilology among their cirrhotic patients [34].

The present study revealed that patients with liver cirrhosis and impaired kidney functions had significantly marked impairment of liver function (lower levels of prothrombin concentration and higher total and direct bilirubin) and electrolytes disturbances (hyponatremia, hyperkalemia, hypermagnesemia and hyperphosphatemia) compa-red to patients with normal kidney function in concordance with the study done by *Ariza et al. in 2015* who found the same results [24] and this explains the association between AKI and the reported increased mortality [2]. Patients with renal impairment had significantly higher MELD and child- Turcotte- Pugh score compared to patients with normal kidney function. These findi-ng were in concordance with *Ariza et al.,2015* [24].

In our study, patients with renal impairment had higher levels of uNGAL than patients with liver cirrhosis without renal impairment. This was in agreement with studies done by *Fagundes et al.* [23], *El-Bassat et al.* [34] and *Gungor et al.* [27].

In the current study among patients with liver cirrhosis and impaired kidney function, there was significant increased uNGAL level among patients with ATN compared to other aetiologies of renal impairment including prerenal azotemia, HRS and CKD. These results were similar to the study done by *Ariza et al.* who studied 12 different novel biomarkers among patients with liver cirrhosis and impaired kidney function and found that uNGAL was the best for differentiation between the different aetiologies of AKI in cirrhosis [24]. Also this agreed with *Treeprasertsuk et al.* who studied uNGAL prospectively in patients with liver cirrhosis with normal creatinine and had AKI prone conditions [25].

The significant higher level of uNGAL found in patients with ATN could be explained by the fact that NGAL is a tubular biomarker which is upregulated with tubular injury. Therefore HRS which is characterized by marked renal vasoconst-riction without significant tubular dysfunction was associated with lower levels of uNGAL [35].

In the current study, level of uNGAL was significantly higher in patients with HRS compared to patients with prerenal azotemia. This finding were similar to that reported by *Gungor et al. in 2015* [27]. This may be explained by the fact that HRS is not pure functional pathology and is associated with subtle kidney tubular and glomerular damage. Many studies reported that this was seen only by electron microscopy [28, 36] perhaps resulting from the cellular changes associated with chronic activation of angiotensin-aldosterone signaling [37]. It is conceivable that profound renovascular constriction may cause subclinical tubular damage in at least a subset of nephrons [38].

None of the traditional biomarkers (i.e. serum creatinine, urea, fractional sodium, urinary potas-sium, urine analysis, microalbuminurea or CrCl by MDRD) showed significant difference between patients with ATN, Prerenal azotemia, HRS and

CKD. These results were agreed by *Verna et al.* who reported that SCr was significantly higher in patients with AKI compared to those with normal kidney function, but statistically similar to those with prerenal azotemia and HRS [26].

This study revealed that patients with AKI associated with active bacterial infection other than urinary tract infection (UTI) had none significantly higher of levels of uNGAL compared with those with AKI in the absence of infections. This was in agreement with the study by *Fagundes et al.; Verna et al.; and El-Bassat et al.* who reported statistically nonsignificant differe-nces in uNGAL between patients with HRS in the presence of infections other than urinary tract infection and those without infections [23,26, 34].

In contrast, *Garcia-Tsao et al* reported significantly higher levels of uNGAL in patients with HRS and infection than those without infection [1].

Patient with cirrhosis and CKD with acute exacer-bation had uNGAL level significantly higher than those with CKD in absence of exacerbation. That was supported by the study done by *Bolignano et al. and Lin et al.* [39, 40].

Many studies reported that malignancies were associated with higher level of NGAL levels [41-43]. In contradictory, in the present study, patients with renal impairment without malignancies had significantly higher levels of uNGAL compared to those with malignancies. There was a positive correlation between uNGAL and serum urea and proteinurea.

In the present study, 50 patients required ICU admission. Their mean uNGAL level was significantly higher compared to those who did not require ICU admission. In this study, thirty four (41%) patients died during their hospital stay due to liver cirrhosis-related complication, of them 7 (11%) patients required HD. Mortality was higher for patients with HRS (38% of all patients mortality and 87% of patients with HRS) followed by patients with ATN (35% of all patients mortality and 75% of patients with ATN). In our study the mean±SD of uNGAL was significantly greater in patients who died compared to those who survived until discharge. This was supported by other studies which found that uNGAL was a good predictor of mortality in different settings [23,26, 44].

Level of uNGAL with cutoff value of 33 ng/ml was able of to detect diagnosis of AKI with sensitivity (79%) and specificity (90%). while a cutoff value of 57 ng/ml showed sensitivity (63.3%) and specificity (90%) for prediction of poor prognosis (patients required dialysis, reported short term mortality or the need for ICU admission).

Treeprasertsuk et al. validated a cut off value of uNGAL of 56 ng/ml for AKI diagnosis providing 77.1 % sensitivity, 73.3 % specificity, 54 % positive predictive value (PPV), 88.7 % negative predictive value (NPV) and a cutoff value of 136.8 ng/ml for diagnosis of ATN with a sensitivity (88.9%) and specificity (80.4%) [25].

These slightly lower levels may be explained as we excluded patients with UTI from our study. In contradictory, *Treeprasertsuk et al* who did not exclude UTI of their study and they found significantly higher levels of uNGAL in cirrhotic patients with AKI in presence of UTI in comp-arison with cirrhotics with AKI and without UTI.

Moreover, in univariate regression analysis model for evaluation of the association of uNGAL with vlalues above 57 ng/ml, serum creatinine, MELD and Child-Pugh scores with short term patient mortality showed that they were significantly associated with short term mortality. Wherever, in multivariate regression analysis of them, uNGAL and Child-pugh score were independant predictor of mortality.

Few studies reported the role of uNGAL in prediction of mortality. Of them, *Verna et al.* reported that uNGAL was an independent predictor of inpatient mortality in patients with liver cirrhosis [26], *Baretto et al.* showed that uNGAL was an independent 3-month mortality predictor in cirrhotic patients with AKI and bacterial infection [44]. However, *Treeprasertsuk et al.* reported that uNGAL was an independent predictor of 30-day mortality [25].

In this study, the level of uNGAL of 94 ng/ml had sensitivity (82.2%) and specificity (87.7%) for the diagnosis of ATN. This suggests that uNGAL is of value in the differential diagnosis of ATN from other types of renal impairment in cirrhosis, including Prerenal- AKI, HRS and CKD.

Conclusion and Recommendation

UNGAL is a promising biomarker for detection of AKI in liver cirrhosis and can help in differentiation between different aetiologies of AKI including ATN, HRS and prerenal azotemia. Moreover, uNGAL can independently predict poor prognosis including the need for ICU admission, the need for dialysis or short-term inpatient mortality in patients with liver cirrhosis.

We recommend larger cohort studies to be conducted to better define the role of uNGAL in diagnosis and prognosis of of AKI in liver cirrhosis, especially in the setting of infection.

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